Appendix A

Sub Chapter 440
New Drugs

Sec. 440.100 Marketed New Drugs Without Approved NDAs or ANDAs (CPG 7132c.02)

BACKGROUND:

Prior policy under the DESI program had permitted a firm to market a new product upon the submission of a New Drug Application (NDA) or Abbreviated New Drug Application (ANDA) as long as the new product was identical to a prescription drug product that had been evaluated as "effective". The history and justification for this approach were described in a FEDERAL REGISTER notice published on June 20, 1975 (40 FR 26142, see paragraph I(D)(5) on pp. 26144-45). This policy was challenged and overturned in a lawsuit on July 29, 1975 (Hoffman-La Roche v. Weinberger, 425 F. Supp. 890 (D.D.C. 1975)). The Court held that if FDA had declared a prescription drug product to be a "new drug", the agency could not permit any identical, similar, or related product to be marketed without prior approval of an NDA or ANDA. The complete text of this decision was published in a FEDERAL REGISTER notice on September 22, 1975 (40 FR 43531). Subsequently, the Court granted certain exceptions to this ruling, but these exceptions are not applicable to DESI effective drugs. The amendment to the Court's order was published in the FEDERAL REGISTER on March 2, 1976 (41 FR 9001). It should be noted that all drugs in the DESI review are "new drugs" under the law.

As a result of this decision, the agency has reevaluated its policy, the resources available to process NDAs and ANDAs and to handle violations of the law, and the alternative policies which might be used to protect the public health and safety within the requirements of the Federal

Food, Drug, and Cosmetic Act. The agency has decided to reaffirm that all products marketed as drugs under the DESI program are new drugs, and therefore, require an approved NDA or ANDA for marketing. In view of the reaffirmation of this policy, the agency must proceed to remove from the market all current DESI-effective prescription products that are not the subjects of approved NDA's or ANDA's, and to prevent in the future the marketing of such unapproved products.

The agency is aware that many firms are marketing products without approved new drug applications that are related to DESI effective prescription drugs. In order to achieve uniform compliance with the Court Order, all violative products must be identified and removed from the market. With the resources presently available for attaining industry-wide compliance, this goal will take several years to achieve. Considering the magnitude of the problem, the limitation on FDA's resources, and the resulting long time period before compliance can be fully attained, the agency has developed a strategy to handle unapproved products on a priority basis. The priorities for enforcement action relate to a particular drug's effect on public health and safety, and are designed to have a maximum impact on violative products and to provide equitable treatment among competing firms. This strategy also integrates with ongoing compliance programs directed at DESI-effective prescription drugs, OTC Category II products, and post-1962 NDA prescription drugs, and anticipated compliance programs directed at DESI-Paragraph XIV prescription drugs (those requiring additional studies before a decision on effectiveness can be made), and pre-1962 new drugs which were not part of DESI.

POLICY:

Part A of this section outlines the sequence for relating drugs for which final determinations have been made regarding their new drug status and for which FEDERAL REGISTER notices have been published requiring ANDA or NDA approval for marketing them. All products within each category will be treated in the same fashion regardless of the size of the firm.

The Center for *Drug Evaluation and Research* will implement Part A of this policy by identifying those marketed drug products which are within the Part A categories named below. The District Offices will then initiate regulatory action against any violative products on the market in accordance with a Compliance Program regarding that specific category of drugs. This procedure will be repeated for each category until overall compliance is achieved. The *CDER* may from time to time add drugs to any category.

Part B of this section covers the regulation of those drugs for which final determinations regarding their regulatory or legal status have not been made.

1. DESI PRESCRIPTION DRUGS WHERE FINAL DETERMINATIONS ON EFFECTIVENESS HAVE BEEN MADE.

   Category I - Ineffective Drugs

   These are covered by an ongoing program (C. P. 7352.001) and will remain top priority.

   Category II - Bio-Problem Drugs

   This category consists of DESI-effective prescription drugs with known or potential bioavailability or bioequivalence problems.

   Approximately 171 drug entities have been identified in this group. Regulatory action has already been initiated on those identical drugs identified in the DHHS Publication No. (FDA) 76-3009 (revised 6/76). The General Program (C.P. 7352.002) covering this category has issued and follow-up to this category is ongoing under Compliance Program Circular PC 7352.002D.

Category III - Top 200 Prescription Drugs

This category consists of the "Top 200" most widely prescribed drugs that have been DESI-rated as effective. This category does not include antibiotics, topical preparations, and those drugs listed in Categories I and II.

An initial survey indicated that there were approximately 25 drug entities in this category requiring attention. These "Top 200 Prescription Drugs" are identified in Program Circular 7352.002E. Regulatory Letters have issued from District offices to all known manufacturers of unapproved drugs subject to this category.

Category IV - Bio-Related Drugs

This category consists of all the prescription drugs related to those in Category II (i.e., drugs containing one or more of the listed ingredients). This category includes combinations, related chemical forms and related dosage forms, including controlled release. It excludes topical preparations. Controlled release preparations may warrant separate attention but this requires further evaluation. These "bio-related drugs" have been handled under Program Circular 7352.002C and regulatory letters have issued to all known manufacturers of unapproved drugs subject to this category.

Category V - Other Identical DESI-Effective Prescription Drugs

This category consists of those products that are identical to DESI-effective prescription drugs, excluding topical preparations, and are not covered by the preceding categories. These products will be handled under a Compliance Program similar to that used for Category II.

Category VI - Other Related DESI-Effective Prescription Drugs

This category consists of combinations and related chemical dosage forms including controlled release. It excludes topical preparations. Products subject to this category will be handled under a Compliance Program similar to that used for Category II.

Category VII - DESI Effective Prescription Topical Preparations Identical and Related

This category consists of all the topical preparations for the drugs covered in Categories I-VI. These products will be handled under a Compliance Program similar to that used for Category II.

B. DESI AND OTHER PRE-1962 PRESCRIPTION DRUGS WHERE FINAL DETERMINATIONS ON THEIR REGULATORY OR LEGAL STATUS HAVE NOT BEEN MADE.

These drugs are covered by the categories outlined below and may be worked into the regulatory scheme described under Part A above as final determinations are made regarding their effectiveness, new drug status, or grandfather status.

DESI "Paragraph XIV" Prescription Drugs.

This category consists of prescription drugs that are currently exempted from regulatory action under Judge Bryant's Order. As final determinations are made regarding the effectiveness of these drugs, they will be handled under the appropriate Part A category on a continuing basis. That is, if a drug is downgraded to "ineffective" it will be handled under Category I, and if it is upgraded to "effective" it will be handled under one of the remaining Part A categories.

DESI "Less-Than-Effective" Prescription Drugs.

This category consists of prescription drugs for which final DESI determinations on

effectiveness have not been made (e.g., possibly or probably effective drugs and those with current NOHs), other than those in the Paragraph XIV Category. As final determinations are made regarding the effectiveness of these drugs, they will be handled under the appropriate Part A category on a continuing basis.

Pre-1962 Prescription Drugs Covered by an NDA But Not Yet Reviewed by DESI.

A certain number of drugs covered by pre-1962 NDA's have not undergone a DESI review. Procedures are being implemented so that these drugs will be evaluated to determine their effectiveness. As final determinations are made on these drugs, they will be handled under the appropriate Part A category on a continuing basis.

Pre-1962 Prescription Drugs Not Covered by an NDA.

A certain number of drug products containing one or more active ingredients first introduced into the marketplace before 1962 are not covered by an NDA. These products are marketed based on their manufacturers' belief that such products are not subject to the new drug provisions of the act. Procedures will be implemented so that these products will be evaluated to determine whether the new drug provisions are applicable to them. If a final determination is made that a particular drug in this category requires an approved NDA or ANDA before marketing, the drug will be handled under the appropriate Part A category on a continuing basis.

POLICY GUIDELINE EXCEPTIONS:

While this policy guide represents a systematic approach to the implementation of the Court Order and the requirements of the new drug provisions of the act, it is not meant to preclude taking action against drugs outside of the established priorities under the following circumstances:

1. Including a new drug (505) charge (where appropriate) for a drug subject to this policy which become violative under another provision of the act.

2. Initiating regulatory action (as a new drug) against any drug subject to this policy should the agency receive significant new information which questions the safety or effectiveness of the drug.

3. Initiating regulatory action against any drug on the market without an approved new drug application if it is identical or related to a post-1962 NDA approved for safety and effectiveness or it contains a new chemical entity not previously marketed.

4. Initiating regulatory action against an unapproved prescription drug product first marketed after November 13, 1984, if the product differs from a product covered by Part B above in:

   A. formulation (as described below);

   B. dosage or strength;

   C. dosage form;

   D. route of administration;

   E. indications for use; or

   F. intended patient population.

   A formulation will be considered different, if:

   (1) the product contains a different active ingredient;

   (2) the product contains a different quantity of an active ingredient;

(3) the product is a non-oral dosage form other than a topical preparation and it contains one or more different inactive ingredients, different amounts of inactive ingredients, or different proportions of inactive ingredients to the extent that the names, amounts, or proportions of inactive ingredients are required by regulation to be disclosed in labeling (see 21 CFR 201.100(b)(5)); or

(4) the product is an oral dosage form or a topical preparation and it contains one or more inactive ingredients not customarily used in such product.

Differences that result from compliance with a compendial standard or an FDA requirement will not cause a product to be subject to this exception.

5. Initiating regulatory action against an unapproved prescription drug product covered by Part B above, if after November 13, 1984, a change is made in:

   A. the product's formulation (as described below);

   B. the product's dosage or strength;

   C. the product's dosage form;

   D. the product's route of administration;

   E. the product's indications for use; or

   F. the product's intended patient population.

A formulation will be considered different, if:

(1) the product contains a different active ingredient;

(2) the product contains a different quantity of an active ingredient;

(3) the product is a non-oral dosage form other than a topical preparation and it contains one or more different inactive ingredients, different amounts of inactive ingredients, or different proportions of inactive ingredients to the extent that the name, amounts, or proportions of inactive ingredients are required by regulation to be disclosed in labeling (see 21 CFR 201.100(b)(5)); or

(4) the product is an oral dosage form or a topical preparation and it contains one or more inactive ingredients not customarily used in such a product.

Changes that are made to comply with a compendial standard or an FDA requirement will not cause a product to be subject to this exception.

6 Initiating regulatory action against an unapproved drug product if a manufacturer, packer, or distributor fails to keep records or make reports regarding adverse drug reactions as required by Section 301.305.

Aside from the exceptions mentioned above, the agency will adhere to the priorities as established. In addition, the *CDER* will deny FDA approval for contract purchase by other Federal government agencies (DOD, VA, PHS) of any drug subject to this policy which does not have an approved NDA or ANDA.

Material between asterisks is new or revised

Based on final rule published in Federal Register of 9/2/86 (51 FR 1476)

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